

SUPPORT FOR THE AMENDMENTS

Claims 1-8, 13, and 24 were previously canceled.

Claims 10, 21, 31-40, 42-44, and 46 are canceled herein.

Claims 9, 11, 14, 16, 20, 22, 25, 27, 41, 45, and 47 have been amended.

Claims 48-60 have been added.

Support for the amendment of Claims 9, 11, 14, 16, 20, 22, 25, 27, 41, 45, and 47 and the introduction of new Claims 48-60 is provided by the specification as originally filed at pages 4-8, for example at page 4, lines 18 to page 5, line 6, page 5, lines 13-19, page 6, lines 8-26, and page 7, line 23 to page 8, line 10, and by the Examples, for example Examples 2-4 and 6 (see also Table 1 on page 9).

No new matter has been added by the present amendments.

REMARKS

Claims 9, 11, 12, 14-20, 22, 23, 25-30, 41, 45, and 47-60 are pending in the present application.

The rejection of Claims 9-12, 14-23, and 25-47 under 35 U.S.C. §103(a) over Baldacci in view of Takayama et al and Noel, is obviated in part by amendment and traversed in part.

The presently claimed invention provides a method of (a) enhancing the production of nitric oxide in a subject in need thereof (see Claim 9 and claims dependent therefrom), or (b) enhancing the production nitric oxide synthase in a living body in a subject in need thereof (see Claim 20 and claims dependent therefrom), by administering to said subject in need thereof an effective amount of pyrrolidonecarboxylic acid in the form of a salt with arginine, wherein said subject in need thereof is in need of improvement or promotion of blood circulation in skin. The presently claimed invention also provides a method of improving or promoting blood circulation in the skin of a subject in need thereof comprising administering to said subject in need thereof an effective amount of a composition comprising pyrrolidonecarboxylic acid in the form of a salt with arginine (see Claim 41 and claims dependent therefrom), as well as a method of improving of the appearance of black rings beneath the eyes in a subject in need thereof comprising administering to said subject in need thereof an effective amount of a composition comprising pyrrolidonecarboxylic acid in the form of a salt with arginine (see Claim 53 and claims dependent therefrom).

Notably, as set forth in the response filed on September 11, 2006, the only patients to whom the claimed compounds are administered in Baldacci (even when combined with Noel) are those in need of restoration of depressed immunodefenses. However, at no point do

Baldacci or Noel, disclose or suggest a role for the claimed composition in the methods as presently claimed. Specifically, neither Baldacci, nor Noel, individually or combined, disclose or suggest the specific sub-set of subjects to which the composition is to be administered.

As previously noted, the U.S. Courts have recently held that a method of administering a compound "to a human in need thereof" is properly construed to require that the compound be administered to human with a recognized need to treat the recited disorder (*Jansen v. Rexall Sundown Inc.*, copy submitted with response filed April 28, 2005). To sufficiently distinguish the claimed methods on the basis of the subset of patients to be treated, Applicants have amended the claimed invention to define the subjects in need of enhanced nitric oxide production (Claim 9) or enhanced nitric oxide synthase production (Claim 20) to be those in need of improvement or promotion of blood circulation in skin (see also Claim 41), as well as those in need of improving of the appearance of black rings beneath the eyes (see Claim 53).

Therefore, as in *Jansen*, the claims of the present invention are drawn to administering a specific composition "to a subject in need" of either enhancing the production of nitric oxide or enhancing the production nitric oxide synthase, wherein the specific patient subset is defined, or "to a subject in need" of improving the appearance of black rings beneath the eyes. Therefore, the failure of Baldacci and Noel to disclose or suggest administering a composition within the scope of the present claims to a patient falling within the defined classes of patients with a recognized need to achieve the claimed objective would make the present invention novel and unobvious in view thereof.

The Examiner alleges that the foregoing deficiency is compensated by the disclosure of Takayama et al. In view thereof, the Examiner alleges that the claimed invention would at least be obvious. Applicants disagree.

As noted above, Baldacci only disclose a method for restoring depressed immunodefenses. This method may entail administering to a patient having depressed immunodefenses an immunomodulating composition comprising L-arginine with L-pyrrolidonecarboxylic acid.

On the other hand, Takayama et al do not disclose pyrrolidonecarboxylic acid with a basic amino acid (e.g., arginine). Takayama et al, however, do disclose “PCA salts also have a weak vasodilator action which affects some persons strongly, and therefore *their use in cosmetics is sometimes avoided.*” (see column 2, line 33 to 36 of US 4,025,525). Such a disclosure by Takayama et al *teaches away* from cosmetics application. Applicants submit that MPEP §2141.02 states: “A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Accordingly, Applicants submit that the disclosure by Takayama et al would fail to render the present invention obvious when this disclosure is combined with that of Baldacci and Noel.

Moreover, applicant discloses that the combination of L- pyrrolidonecarboxylic acid and L-arginine has a significant effect on the amount of nitric oxide formed as compared to individual administration of L- pyrrolidonecarboxylic acid or L-arginine. This result is clearly illustrated in Table 1 (see page 9 of the specification) reproduced below:

	Concentrations of the ingredients in the medium (mM)			Formed amount of nitric oxide
	L-Arg	L-PCA	GA	nmol/10 ³ cells
Comparative Example 1	0	0	0	1.1
Comparative Example 2	5	0	0	1.9
Comparative Example 3	5	0	10	2.9
Example 1	0	10	0	1.4
Example 2	5	2.5	0	2.1
Example 3	5	5	0	3.4
Example 4	5	10	0	4.1

In addition to the significant effect on the amount of nitric oxide formed by the combined administration of L- pyrrolidonecarboxylic acid and L-arginine as compared to individual administration of L- pyrrolidonecarboxylic acid or L-arginine demonstrated above, Applicants have also shown that the combined administration of L- pyrrolidonecarboxylic acid and L-arginine has an effect on improvement of black rings beneath eyes (see Example 6). Therefore, even if the cited combination of art were sufficient to establish a prima facie case of obviousness, such a case would be rebutted by the evidence already of record.

Applicants request withdrawal of this grounds of rejection.

Applicants submit that the present application is now in condition for allowance.
Early notification of such action is earnestly solicited.

Respectfully submitted,

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